

In re Application of:
Koo et al.
Application No.: 10/814,981
Filed: March 30, 2004
Page 8

PATENT
Atty Docket No.: INTEL1490(P18518)

Remarks/Arguments

Claims 1-34 were pending prior to this Response. By the present communication, no claims have been added or canceled, and claims 1, 22, 26 and 31 have been amended to define Applicants' invention with greater particularity. Support for the amended claim language may be found in the specification at, among others, paragraphs 0010, 0024, 0026 and 0029. The amendments do not raise any issues of new matter and the amended claims do not present new issues requiring further consideration or search. Accordingly, claims 1-34 are currently pending in this application.

Rejection under 35 U.S.C. § 112, Second Paragraph

Applicants respectfully traverse the rejection of claims 1-34 under 35 U.S.C. § 112, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

With regard to claim 1, the Examiner alleges that use of the limitation "associating" is indefinite because it is unclear how the first specific binding pair member associates with the SERS active particle or substrate, i.e., adsorption, covalent binding, or close proximity. Applicants respectfully submit that the claim as written is not indefinite and that the specification provides ample support for illustrative methods for associating specific binding pair members to surfaces of solid structures. Applicants further submit that the term "associating" is clearly understood by one skilled in the art. For example, "association constant" is defined as, "a quantitative measure of the affinity of a receptor for its ligand (e.g. of the antigen-binding site of an antibody for its cognate antigen). It is determined by Scatchard analysis of equilibrium binding experiments and has the dimensions 1 mol^{-1} ." (The Encyclopedia of Molecular Biology, Ed. Kendrew, 1994). The specification discloses that

[t]o be associated with a SERS-active particle, a first specific binding pair member is attracted to the SERS-active substrate. In association, the first specific binding pair member is placed on or

near the SERS-active substrate by internal force, external force, or thermal drift (e.g. charge attraction, magnetic field, optical pressure, fluidic pressure, or diffusion). (Specification, paragraph 0050).

Non-limiting examples of association include placing in close proximity (Specification, paragraph 0050), adsorption (Specification, paragraph 0051), contacting in the presence of chemical salts (Specification, paragraph 0055), and covalent attachment (Specification, paragraph 0056). Accordingly, Applicants submit that one of skill in the art would understand metes and bounds of the claimed invention. Withdrawal of the rejection is respectfully requested.

With respect to claim 18, the Examiner alleges that there is insufficient antecedent basis for the limitation “the surface-enhanced Raman scattering label is deoxyadenosine monophosphate.” Applicants respectfully direct the Examiner’s attention to the specification at paragraph 0042, which discloses, “[i]n certain aspects, the label is a nucleotide, or any other molecule which yields a strong SERS signal, as disclosed in further detail herein. For example, the SERS label can be deoxy-adenosine monophosphate.” Accordingly, Applicants submit that the limitation is supported by the specification, and respectfully request withdrawal of the rejection.

With respect to claims 22, 26 and 31, the Examiner alleges indefiniteness because it is unclear how an antibody or an immobilized first specific binding pair member can generate any signal if it’s not attached to a label or means to generate a signal. Applicants respectfully direct the Examiner’s attention to the specification at paragraph 0007, which discloses that

[t]he methods disclosed herein *do not require* the labeling process of traditional fluorescent assays, such as immunoassays, used for detecting binding of a first biomolecule to a second biomolecule. Since *labels are not used* and/or fluorescent detection is not employed, the background signal of an assay is greatly reduced. Furthermore, modification of a biomolecule, such as binding a label to a biomolecule, which is difficult and can interfere with the structure and/or activity of the biomolecule, is not necessary. Therefore, by using SERS binding events can be detected without

In re Application of:

Koo et al.

Application No.: 10/814,981

Filed: March 30, 2004

Page 10

PATENT

Atty Docket No.: INTEL1490(P18518)

using fluorescence labels, resulting in an increased sensitivity and increased accuracy. (Emphasis added).

In addition, the specification discloses,

[b]efore association of the first specific binding pair member with a SERS-active substrate or particle, little or no SERS effect is observed, and the Raman signal of the first specific binding pair member, such as an antibody, in certain aspects of the invention, is weak. The SERS signal generated by a first specific binding pair member is strengthened by associating the first specific binding pair member with a SERS-active particle or substrate, for example by adsorbing the first specific binding pair member to a metal particle, after introduction of metal particles and optionally, chemical salts 110. (Specification, Paragraph 0026).

The Specification further discloses that “[t]he first specific binding pair member, such as an antibody, generally generates a strong SERS signal by itself when associated with a SERS-active surface, such as a metal particle.” (Specification, paragraph 0041). Accordingly, Applicants submit that the specification clearly teaches how an antibody or an immobilized first specific binding pair member can generate a SERS signal even if it’s not attached to a label. Withdrawal of the rejection is respectfully requested.

In summary, it is submitted that the subject application clearly teaches the claimed subject matter such that the skilled artisan would have understood the metes and bounds of the claims. Accordingly, withdrawal of the rejection of claims 1-34 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite is respectfully requested.

Rejection under 35 U.S.C. § 102

Applicants respectfully traverse the rejection of claims 1-4, 6-11, 13-17 and 20 under 35 U.S.C. § 102(b) as allegedly being anticipated by Tarcha, et al. (U.S. Patent No. 5,376,556, hereinafter “Tarcha”). The Examiner alleges that Tarcha teaches a method, composition, device and kit for the determination of the presence or amount of an analyte by monitoring an analyte-

mediated ligand binding event in a test mixture which contains the analyte to be assayed, a specific binding member, a Raman-active label and a particulate having a surface for inducing a surface-enhanced Raman light scattering. However, while Tarcha discloses that “the particulate is characterized by having a surface capable of inducing a surface-enhanced Raman light scattering,” Tarcha illuminates “the test mixture with a radiation sufficient to cause the *Raman-active label* in the complex to emit a detectable Raman spectrum....” (Tarcha, col. 6, lines 1-6, emphasis added).

Applicants submit that as claimed, the methods of present invention do not detect a surface-enhanced Raman scattering signal by illuminating the test mixture with a radiation sufficient to cause the Raman-active label. The methods of the present invention are “used to detect interaction between virtually any molecules provided that one of the molecules generates a detectable SERS signal when associated with a SERS-active particle or substrate....”

(Specification, paragraph 0010). As shown in Figure 2,

[a] SERS-active particle or substrate, for example a metal particle 240, is associated with the first specific binding pair member 200. Binding of the first specific binding pair member 200 to the second specific binding pair member 250 can then dissociate the metal particle 240 from the first specific binding pair member 200, resulting in a reduced SERS signal. (Specification, paragraph 0028).

The specification provides a clear distinction between “a surface-enhanced Raman scattering-active particle or substrate” (i.e., a metal particle) and “a label” used to enhance the SERS signal (i.e., a Raman-active label). As disclosed in the specification at paragraph 0029,

[t]he first specific binding pair member 200 *can* be associated with a label 230 to enhance the SERS signal of the first specific binding pair member 200. In other examples, the first specific binding pair member 200 can generate a SERS signal *of its own* when positioned close to the SERS-active particle or surface. (emphasis added).

Accordingly, the present invention does not require use of a label, as defined by Tarcha.

Anticipation under 35 U.S.C. § 102(b) requires that the reference recite each and every element of the claims in a single document. Since Tarcha et al. fails to disclose each and every element of the methods of the invention, as defined by amended claim 1, Applicants respectfully submit that the Examiner has failed to establish anticipation under 35 U.S.C. § 102 (b) over Tarcha et al. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Rejection under 35 U.S.C. § 103

Applicants respectfully traverse the rejection of claim 12 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Tarcha in view of Fray (U.S. Patent No. 4,904,356, hereinafter "Fray"). The burden of proof in establishing a *prima facie* case of obviousness under §103 clearly rests with the Patent Office. *In re Piasecki*, 745 F.2d 1468, 1472 (Fed. Cir. 1984). In establishing a *prima facie* case, the Patent Office, among other things, must show that (1) the prior art would have suggested to those of ordinary skill in the art that they should make the claimed invention and (2) that the prior art would have revealed a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). "Both the suggestion and the reasonable expectation of success must be found in the prior art, not in the applicant's disclosure." *Id.* Thus, "particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed." *In re Kotzab*, 217 F.3d 1365, 1371 (Fed. Cir. 2000). Further, when relying on the knowledge of persons of ordinary skill in the art, the Patent Office must "explain what specific understanding or technological principle within the knowledge of one of ordinary skill in the art would have suggested the combination." *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998). "The factual inquiry whether to combine references must be thorough and searching. It must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with." *In re Sang Su Lee*, 277 F.3d 1338, 1343 (Fed. Cir. 2002) (citations omitted).

To date, the Patent Office has failed to provide objective evidence of any suggestion or motivation in the prior art to combine and modify the particular references cited by the Office. Instead, the Office has simply recited elements gleaned from the various references and stated that the combination of these elements would have been obvious to one skilled in the art. It is well settled that the Patent and Trademark Office cannot pick and choose among the individual elements of assorted prior art references to recreate the claimed invention. *SmithKline Diagnostics, Inc. v. Helena Laboratories Corp.*, 859 F.2d 878, 887 (Fed. Cir. 1988). In addition, it is now well established that “[b]road conclusory statements regarding the teaching of multiple references standing alone are not ‘evidence’.” *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999); see also *In re Kotzab*, 217 F.3d at 1370. “Th[e] factual question of motivation is material to patentability, and [can] not be resolved on subjective belief and unknown authority.” *In re Sang Su Lee* 277 F.3d at 1343-44. Without such objective evidence to combine the references, it is inferred that the references were selected with the assistance of hindsight. *In re Rouffet*, 149 F.3d at 1358. It is well-established that the use of hindsight in the selection of references that comprise a case of obviousness is forbidden. *Id.*

The Examiner alleges that Tarcha teaches a method, composition, device and kit for the determination of the presence or amount of an analyte by monitoring an analyte-mediated ligand binding event in a test mixture which contains the analyte to be assayed, a specific binding member, a Raman-active label and a particulate having a surface for inducing a surface-enhanced Raman light scattering, but also indicates that Tarcha fails to teach that the chemical salt is lithium chloride. However, as discussed above, the methods of Tarcha require a Raman-active label that is illuminated to emit a detectable Raman spectrum. Accordingly, Tarcha fails to suggest a method that includes detecting a change in the surface-enhanced Raman scattering signal that is generated by excitation of the first specific binding pair member associated with the surface-enhanced Raman scattering-active particle or substrate.

The disclosure of Fray does not cure the above-described deficiencies in Tarcha for teaching or suggesting the claimed invention. Fray allegedly discloses use of lithium chloride

In re Application of:

Koo et al.

Application No.: 10/814,981

Filed: March 30, 2004

Page 14

PATENT

Atty Docket No.: INTEL1490(P18518)

salt to saturate a metal surface to allow metal ions to move through freely. Applicants submit that Fray is absolutely silent with regard to generating a surface-enhanced Raman scattering signal, let alone a signal that is generated by excitation of a first specific binding pair member associated with the surface-enhanced Raman scattering-active particle or substrate.

Applicants respectfully submit that one of skill in the art at the time the invention was made would not have found it *prima facie* obvious to combine the disclosures of Tarcha and Fray to arrive at Applicants' invention. However, even if one were motivated to combine Tarcha and Fray, Applicants submit that the proposed combination would result in a method of determining the presence of an analyte by monitoring an analyte-mediated ligand binding in a test mixture that includes a Raman-active label *and* a particulate having a surface for inducing a surface-enhanced Raman light scattering. While the metal surface would indeed be enhanced by treatment with the lithium chloride of Fray, the detected signal would still be generated by illuminating the test mixture with a radiation sufficient to cause the *Raman-active label* in the complex to emit a detectable Raman spectrum. Accordingly, for the reasons provided above, Applicants respectfully request withdrawal of the rejection.

Applicants respectfully traverse the rejection of claim 12 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Tarcha in view of Gole, et al. (U.S. Patent No. 6,589,883, hereinafter "Gole"). The remarks above distinguishing the disclosure of Tarcha from the current invention apply equally here. The Examiner indicates that Tarcha fails to teach that the SERS active substrate is a porous silicon substrate comprising impregnated metals.

Therefore, the Examiner relies upon the disclosure of Gole for metalizing substrates such as porous silicon for use in Raman scattering detection. However, Gole is absolutely silent with regard to generating a surface-enhanced Raman scattering signal that is generated by excitation of a first specific binding pair member associated with the surface-enhanced Raman scattering-active particle or substrate.

Applicants respectfully submit that one of skill in the art at the time the invention was made would not have found it *prima facie* obvious to combine the disclosures of Tarcha and Gole to arrive at Applicants' invention. However, even if one were motivated to combine Tarcha and Gole, Applicants submit that the proposed combination would result in a method of determining the presence of an analyte by monitoring an analyte-mediated ligand binding in a test mixture that includes a Raman-active label *and* a particulate having a surface for inducing a surface-enhanced Raman light scattering. While the Raman-active substrate would have high surface area as a result of Gole's metalized porous silicon, the detected signal would still be generated by illuminating the test mixture with a radiation sufficient to cause the *Raman-active label* in the complex to emit a detectable Raman spectrum. Accordingly, for the reasons provided above, Applicants respectfully request withdrawal of the rejection.

Applicants respectfully traverse the rejection of claims 5, 22-28, 30 and 31-34 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Tarcha in view of Maine, et al. (U.S. Patent No. 6,221,619, hereinafter "Maine"). The remarks above distinguishing the disclosure of Tarcha from the current invention apply equally here. The Examiner indicates that Tarcha fails to teach immobilizing the first specific binding pair member/antibody on an immobilizing substrate.

Therefore, the Examiner relies upon the disclosure of Maine for different assay formats comprising attaching an antibody/antigen to a solid phase such as porous, non-porous materials, latex particles, microparticles, beads, membranes, microtiter wells, and plastic tubes. However, Maine is absolutely silent with regard to generating a surface-enhanced Raman scattering signal that is generated by excitation of a first specific binding pair member associated with the surface-enhanced Raman scattering-active particle or substrate.

Applicants respectfully submit that one of skill in the art at the time the invention was made would not have found it *prima facie* obvious to combine the disclosures of Tarcha and Maine to arrive at Applicants' invention. However, even if one were motivated to combine Tarcha and Maine, Applicants submit that the proposed combination would result in a method of

In re Application of:

Koo et al.

Application No.: 10/814,981

Filed: March 30, 2004

Page 16

PATENT

Atty Docket No.: INTEL1490(P18518)

determining the presence of an analyte by monitoring an analyte-mediated ligand binding in a test mixture that includes a Raman-active label *and* a particulate having a surface for inducing a surface-enhanced Raman light scattering. While the complex formed in the test mixture would be immobilized during the assay, the detected signal would still be generated by illuminating the test mixture with a radiation sufficient to cause the *Raman-active label* in the complex to emit a detectable Raman spectrum. Accordingly, for the reasons provided above, Applicants respectfully request withdrawal of the rejection.

Applicants respectfully traverse the rejection of claim 29 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Tarcha in view of Maine as applied to claims 22-28 and 30-34 above, and further in view of Fray. The remarks above distinguishing the disclosure of Tarcha from the current invention apply equally here. The Examiner indicates that Tarcha and Maine fail to teach that the first specific binding pair is adsorbed on the metal particle in the presence of lithium chloride.

Therefore, the Examiner relies upon the disclosure of Fray for use of lithium chloride salt to saturate a metal surface to allow metal ions to move through freely. However, Applicants submit that Fray is absolutely silent with regard to generating a surface-enhanced Raman scattering signal, let alone a signal that is generated by excitation of a first specific binding pair member associated with the surface-enhanced Raman scattering-active particle or substrate.

Applicants respectfully submit that one of skill in the art at the time the invention was made would not have found it *prima facie* obvious to combine the disclosures of Tarcha, Maine and Fray to arrive at Applicants' invention. However, even if one were motivated to combine Tarcha, Maine and Fray, Applicants submit that the proposed combination would result in a method of determining the presence of an analyte by monitoring an analyte-mediated ligand binding in a test mixture that includes a Raman-active label *and* a particulate having a surface for inducing a surface-enhanced Raman light scattering. While the complex formed in the test mixture would be immobilized during the assay and the surface would indeed be enhanced by treatment with the

In re Application of:

Koo et al.

Application No.: 10/814,981

Filed: March 30, 2004

Page 17

PATENT

Atty Docket No.: INTEL1490(P18518)

lithium chloride, the detected signal would still be generated by illuminating the test mixture with a radiation sufficient to cause the *Raman-active label* in the complex to emit a detectable Raman spectrum. Accordingly, for the reasons provided above, Applicants respectfully request withdrawal of the rejection.

In re Application of:

Koo et al.

Application No.: 10/814,981

Filed: March 30, 2004

Page 18

PATENT

Atty Docket No.: INTEL1490(P18518)

Conclusion

In summary, for the reasons set forth herein, Applicants maintain that claims 1-34 clearly and patentably define the invention and respectfully request that the Examiner withdraw all rejections and pass the application to allowance. If the Examiner would like to discuss any of the issues raised in the Office Action, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

No fee is deemed necessary in connection of the filing of this document. However, the Commissioner is hereby authorized to charge for any additional required fees, or credit any overpayments to Deposit Account No. 07-1896.

Respectfully submitted,



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Date: October 3, 2005

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